

**Clinical trial results:****Efficacy, Safety, and Tolerability of Ezetimibe in Coadministration With Simvastatin in the Therapy of Adolescents With Heterozygous Familial Hypercholesterolemia****Summary**

EudraCT number	2004-002627-40
Trial protocol	FI AT DE IT ES Outside EU/EEA
Global end of trial date	25 June 2007

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	20 May 2015

Trial information**Trial identification**

Sponsor protocol code	P02579
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00129402
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000007-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 June 2007
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2007
Global end of trial reached?	Yes
Global end of trial date	25 June 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to test the hypothesis that in adolescent participants with heterozygous familial hypercholesterolemia (HeFH) the reduction in Low-Density-Lipoprotein Cholesterol (LDL-C) from baseline to 6 weeks measured as percent change in the pooled groups assigned to receive randomized treatment with ezetimibe (EZ) plus simvastatin 10 mg, 20 mg, or 40 mg will be greater compared with the reduction of LDL-C in the pooled groups assigned to receive randomized treatment with simvastatin 10 mg, 20 mg, or 40 mg as monotherapy.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 August 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Canada: 53
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	Colombia: 14
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Netherlands: 55
Country: Number of subjects enrolled	South Africa: 38
Country: Number of subjects enrolled	United States: 36

Worldwide total number of subjects	248
EEA total number of subjects	93

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	23
Adolescents (12-17 years)	225
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study enrolled adolescents (age ≥ 10 to ≤ 17 years) of either sex and of any race, Tanner Stage II or higher, body weight at least 40 kg and above 10th percentile. Girls were to be postmenarchal, defined as at least 1 year after first menstrual period and having had at least 3 menstrual periods. Other inclusion and exclusion criteria applied.

Period 1

Period 1 title	Period 1 - Week 1 to Week 6
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Ezetimibe 10 mg + Simvastatin 10 mg

Arm description:

Participants received ezetimibe 10 mg plus simvastatin 10 mg orally once daily for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	SCH 058235, MK-0653
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one 10-mg tablet orally once daily.

Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one 10-, 20-, or 40-mg tablet, orally once daily.

Arm title	Ezetimibe 10 mg + Simvastatin 20 mg
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Arm description:

Participants received ezetimibe 10 mg plus simvastatin 20 mg orally once daily for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	SCH 058235, MK-0653
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one 10-mg tablet orally once daily.

Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: one 10-, 20-, or 40-mg tablet, orally once daily.	
Arm title	Ezetimibe 10 mg + Simvastatin 40 mg
Arm description: Participants received ezetimibe 10 mg plus simvastatin 40 mg orally once daily for 6 weeks.	
Arm type	Experimental
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	SCH 058235, MK-0653
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: one 10-mg tablet orally once daily.	
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: one 10-, 20-, or 40-mg tablet, orally once daily.	
Arm title	Simvastatin 10 mg
Arm description: Participants received simvastatin monotherapy 10 mg plus placebo for EZ 10 mg orally, once daily for 6 weeks.	
Arm type	Active comparator
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: one 10-, 20-, or 40-mg tablet, orally once daily.	
Investigational medicinal product name	Placebo to Match Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: one placebo tablet orally, once daily.	
Arm title	Simvastatin 20 mg
Arm description: Participants received simvastatin 20 mg plus placebo for EZ 10 mg orally, once daily for 6 weeks.	
Arm type	Active comparator

Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: one 10-, 20-, or 40-mg tablet, orally once daily.	
Investigational medicinal product name	Placebo to Match Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: one placebo tablet orally, once daily.	
Arm title	Simvastatin 40 mg

Arm description:

Participants received simvastatin monotherapy 40 mg plus placebo for EZ 10 mg orally, once daily for 6 weeks.

Arm type	Active comparator
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: one 10-, 20-, or 40-mg tablet, orally once daily.	
Investigational medicinal product name	Placebo to Match Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
one placebo tablet orally, once daily.

Number of subjects in period 1	Ezetimibe 10 mg + Simvastatin 10 mg	Ezetimibe 10 mg + Simvastatin 20 mg	Ezetimibe 10 mg + Simvastatin 40 mg
Started	43	40	43
Completed	43	39	41
Not completed	0	1	2
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	1	1
Lost to follow-up	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Simvastatin 10 mg	Simvastatin 20 mg	Simvastatin 40 mg
Started	40	40	42

Completed	39	39	40
Not completed	1	1	2
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	1
Lost to follow-up	-	-	1
Protocol deviation	1	-	-

Period 2

Period 2 title	Period 2 - Week 7 to Week 33
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
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Arm title	Ezetimibe 10 mg + Simvastatin 40 mg
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Arm description:

Participants who received 10-mg ezetimibe coadministered with either 10-, 20-, or 40-mg simvastatin in Period 1 and received 10 mg ezetimibe coadministered with 40-mg simvastatin once daily for 27 weeks in Period 2.

Arm type	Experimental
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	SCH 058235, MK-0653
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one 10-mg tablet orally once daily.

Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one 10-, 20-, or 40-mg tablet, orally once daily.

Arm title	Simvastatin 40 mg
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Arm description:

Participants who received either 10-, 20-, or 40-mg simvastatin monotherapy in Period 1 and received 40-mg simvastatin and placebo to match ezetimibe once daily for 27 weeks in Period 2.

Arm type	Active comparator
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one 10-, 20-, or 40-mg tablet, orally once daily.

Investigational medicinal product name	Placebo to Match Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one placebo tablet orally, once daily.

Number of subjects in period 2^[1]	Ezetimibe 10 mg + Simvastatin 40 mg	Simvastatin 40 mg
Started	122	118
Completed	114	113
Not completed	8	5
Laboratory Adverse Event	-	1
Consent withdrawn by subject	1	3
Laboratory Adverse Event	3	-
Adverse event, non-fatal	2	-
Lost to follow-up	1	-
Protocol deviation	1	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One participant who completed Period 1 did not enter Period 2. Participant did enter and complete Period 3.

Period 3

Period 3 title	Period 3 - Long-Term Experience
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ezetimibe + simvastatin - Long Term Experience
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Arm description:

All participants, regardless of assigned treatment groups in Periods 1 and 2 initially received open-label simvastatin 10 or 20 mg (based upon physician judgment for the treatment of the individual participant) and ezetimibe 10 mg for 20 weeks. The continued simvastatin dose may have been adjusted based on response and titrated up to 20 mg or 40 mg as necessary, based upon response and in accordance with National Cholesterol Education Program guidelines. Similarly, the dose of simvastatin 20 or 40 mg may be titrated downward as necessary.

Arm type	Experimental
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	SCH 058235, MK-0653
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one 10-mg tablet orally once daily.

Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one 10-, 20-, or 40-mg tablet, orally once daily.

Number of subjects in period 3^[2]	Ezetimibe + simvastatin - Long Term Experience
Started	226
Completed	222
Not completed	5
Participant moved	1
Consent withdrawn by subject	3
Protocol deviation	1
Joined	1
Completer from Period 1	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One participant who completed Period 1 did not enter Period 2. Participant did enter and complete Period 3.

Baseline characteristics

Reporting groups

Reporting group title	Ezetimibe 10 mg + Simvastatin 10 mg
Reporting group description:	Participants received ezetimibe 10 mg plus simvastatin 10 mg orally once daily for 6 weeks.
Reporting group title	Ezetimibe 10 mg + Simvastatin 20 mg
Reporting group description:	Participants received ezetimibe 10 mg plus simvastatin 20 mg orally once daily for 6 weeks.
Reporting group title	Ezetimibe 10 mg + Simvastatin 40 mg
Reporting group description:	Participants received ezetimibe 10 mg plus simvastatin 40 mg orally once daily for 6 weeks.
Reporting group title	Simvastatin 10 mg
Reporting group description:	Participants received simvastatin monotherapy 10 mg plus placebo for EZ 10 mg orally, once daily for 6 weeks.
Reporting group title	Simvastatin 20 mg
Reporting group description:	Participants received simvastatin 20 mg plus placebo for EZ 10 mg orally, once daily for 6 weeks.
Reporting group title	Simvastatin 40 mg
Reporting group description:	Participants received simvastatin monotherapy 40 mg plus placebo for EZ 10 mg orally, once daily for 6 weeks.

Reporting group values	Ezetimibe 10 mg + Simvastatin 10 mg	Ezetimibe 10 mg + Simvastatin 20 mg	Ezetimibe 10 mg + Simvastatin 40 mg
Number of subjects	43	40	43
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	14.1 ± 1.8	14 ± 2	14 ± 2
Gender categorical Units: Subjects Female Male	18 25	17 23	18 25

Reporting group values	Simvastatin 10 mg	Simvastatin 20 mg	Simvastatin 40 mg
Number of subjects	40	40	42
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	14.5 ± 1.8	14.1 ± 2.1	14.4 ± 1.5
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Gender categorical Units: Subjects			
Female	17	18	18
Male	23	22	24

Reporting group values	Total		
Number of subjects	248		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	106		
Male	142		

End points

End points reporting groups

Reporting group title	Ezetimibe 10 mg + Simvastatin 10 mg
Reporting group description:	Participants received ezetimibe 10 mg plus simvastatin 10 mg orally once daily for 6 weeks.
Reporting group title	Ezetimibe 10 mg + Simvastatin 20 mg
Reporting group description:	Participants received ezetimibe 10 mg plus simvastatin 20 mg orally once daily for 6 weeks.
Reporting group title	Ezetimibe 10 mg + Simvastatin 40 mg
Reporting group description:	Participants received ezetimibe 10 mg plus simvastatin 40 mg orally once daily for 6 weeks.
Reporting group title	Simvastatin 10 mg
Reporting group description:	Participants received simvastatin monotherapy 10 mg plus placebo for EZ 10 mg orally, once daily for 6 weeks.
Reporting group title	Simvastatin 20 mg
Reporting group description:	Participants received simvastatin 20 mg plus placebo for EZ 10 mg orally, once daily for 6 weeks.
Reporting group title	Simvastatin 40 mg
Reporting group description:	Participants received simvastatin monotherapy 40 mg plus placebo for EZ 10 mg orally, once daily for 6 weeks.
Reporting group title	Ezetimibe 10 mg + Simvastatin 40 mg
Reporting group description:	Participants who received 10-mg ezetimibe coadministered with either 10-, 20-, or 40-mg simvastatin in Period 1 and received 10 mg ezetimibe coadministered with 40-mg simvastatin once daily for 27 weeks in Period 2.
Reporting group title	Simvastatin 40 mg
Reporting group description:	Participants who received either 10-, 20-, or 40-mg simvastatin monotherapy in Period 1 and received 40-mg simvastatin and placebo to match ezetimibe once daily for 27 weeks in Period 2.
Reporting group title	Ezetimibe + simvastatin - Long Term Experience
Reporting group description:	All participants, regardless of assigned treatment groups in Periods 1 and 2 initially received open-label simvastatin 10 or 20 mg (based upon physician judgment for the treatment of the individual participant) and ezetimibe 10 mg for 20 weeks. The continued simvastatin dose may have been adjusted based on response and titrated up to 20 mg or 40 mg as necessary, based upon response and in accordance with National Cholesterol Education Program guidelines. Similarly, the dose of simvastatin 20 or 40 mg may be titrated downward as necessary.
Subject analysis set title	Ezetimibe + Simvastatin - Pooled
Subject analysis set type	Intention-to-treat
Subject analysis set description:	All participants who received randomized treatment assignment, had at least one baseline assessment, and had had evaluable data for endpoint. Data for participants randomly assigned to receive ezetimibe 10 mg coadministered with simvastatin 10, 20, or 40 mg were pooled.
Subject analysis set title	Simvastatin Monotherapy - Pooled
Subject analysis set type	Intention-to-treat
Subject analysis set description:	All participants who received randomized treatment assignment, had at least one baseline assessment, and had evaluable data for endpoint. Data for participants randomly assigned to simvastatin 10, 20, or 40 mg monotherapy were pooled.

Primary: Percentage Change from Baseline in Low-density Lipoprotein Cholesterol (LDL-C) at Week 6

End point title	Percentage Change from Baseline in Low-density Lipoprotein Cholesterol (LDL-C) at Week 6
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End point description:

LDL-C levels calculated at baseline and after 6 weeks of treatment. LDL-C determined by the Friedewald equation (LDL-C = Total Cholesterol – [Triglyceride/5] – High-density Lipoprotein Cholesterol). Least-square means and standard errors calculated using an analysis of variance (ANOVA) model that extracted effects due to treatment (ezetimibe 10 mg, placebo), dose (simvastatin 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.

End point type	Primary
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End point timeframe:

Baseline and Week 6

End point values	Ezetimibe + Simvastatin - Pooled	Simvastatin Monotherapy - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126	120		
Units: Percentage Change				
least squares mean (standard error)	-49.45 (± 1.19)	-34.43 (± 1.22)		

Statistical analyses

Statistical analysis title	Difference in Percentage Change from Baseline
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Statistical analysis description:

Statistical comparison performed using an ANOVA model that extracts effects due to treatment (EZ 10 mg, placebo), dose (simva 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.

Comparison groups	Ezetimibe + Simvastatin - Pooled v Simvastatin Monotherapy - Pooled
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	ANOVA
Parameter estimate	Difference in Least-squares Means
Point estimate	-15.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.36
upper limit	-11.7

Secondary: Percentage Change from Baseline in Total Cholesterol (TC)

End point title	Percentage Change from Baseline in Total Cholesterol (TC)
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End point description:

Serum TC levels measured using at baseline and after 6 weeks of study drug administration. Least-square means and standard errors calculated using an analysis of variance (ANOVA) model that extracted effects due to treatment (ezetimibe 10 mg, placebo), dose (simvastatin 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.

End point type Secondary

End point timeframe:

Baseline and Week 6

End point values	Ezetimibe + Simvastatin - Pooled	Simvastatin Monotherapy - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126	120		
Units: Percentage Change				
least squares mean (standard error)	-38.23 (\pm 0.96)	-26.28 (\pm 0.99)		

Statistical analyses

Statistical analysis title Difference in Percentage Change from Baseline

Statistical analysis description:

Statistical comparison performed using an ANOVA model that extracts effects due to treatment (ezetimibe 10 mg, placebo), dose (simvastatin 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.

Comparison groups	Simvastatin Monotherapy - Pooled v Ezetimibe + Simvastatin - Pooled
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	ANCOVA
Parameter estimate	Difference in Least-square means
Point estimate	-11.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.65
upper limit	-9.26

Secondary: Percentage Change from Baseline in Non High-density Lipoprotein Cholesterol (non HDL-C)

End point title Percentage Change from Baseline in Non High-density Lipoprotein Cholesterol (non HDL-C)

End point description:

Serum Non-HDL-C calculated at baseline and after 6 weeks of study drug administration. Least-square means and standard errors calculated using an analysis of variance (ANOVA) model that extracted effects due to treatment (ezetimibe 10 mg, placebo), dose (simvastatin 10 mg, 20 mg, and 40 mg), treatment

by dose interaction, and sex effects.

End point type	Secondary
End point timeframe:	
Baseline and Week 6	

End point values	Ezetimibe + Simvastatin - Pooled	Simvastatin Monotherapy - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126	120		
Units: Percentage Change				
least squares mean (standard error)	-46.84 (\pm 1.13)	-32.68 (\pm 1.16)		

Statistical analyses

Statistical analysis title	Difference in Percentage Change from Baseline
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Statistical analysis description:

Statistical comparison performed using an ANOVA model that extracts effects due to treatment (ezetimibe 10 mg, placebo), dose (simvastatin 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.

Comparison groups	Ezetimibe + Simvastatin - Pooled v Simvastatin Monotherapy - Pooled
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	ANOVA
Parameter estimate	Difference in Least-squares means
Point estimate	-14.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.32
upper limit	-11

Secondary: Percentage Change from Baseline in Triglycerides (TG)

End point title	Percentage Change from Baseline in Triglycerides (TG)
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End point description:

Serum TG levels measured at baseline and after 6 weeks of study drug administration.

End point type	Secondary
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End point timeframe:

Baseline and Week 6

End point values	Ezetimibe + Simvastatin - Pooled	Simvastatin Monotherapy - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126	120		
Units: Percentage Change				
median (standard deviation)	-16.56 (\pm 30.26)	-12.28 (\pm 31.49)		

Statistical analyses

Statistical analysis title	Difference in Percentage Change from Baseline
Statistical analysis description:	
Analyzed using ANOVA on the ranks extracting effects due to treatment (ezetimibe, placebo) and sex.	
Comparison groups	Ezetimibe + Simvastatin - Pooled v Simvastatin Monotherapy - Pooled
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	non-parametric model
Parameter estimate	Hodges-Lehmann Method
Point estimate	-2.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.09
upper limit	4.12

Secondary: Percentage Change from Baseline in Apolipoprotein B (Apo B)

End point title	Percentage Change from Baseline in Apolipoprotein B (Apo B)
End point description:	
Serum Apo B measured at baseline and after 6 weeks of study drug administration. Least-square means and standard errors calculated using an analysis of variance (ANOVA) model that extracted effects due to treatment (ezetimibe 10 mg, placebo), dose (simvastatin 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.	
End point type	Secondary
End point timeframe:	
Baseline and Week 6	

End point values	Ezetimibe + Simvastatin - Pooled	Simvastatin Monotherapy - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	118		
Units: Percentage Change				
least squares mean (standard error)	-38.92 (\pm 1.1)	-26.69 (\pm 1.11)		

Statistical analyses

Statistical analysis title	Difference in Percentage Change from Baseline
Statistical analysis description:	
Statistical comparison performed using an ANOVA model that extracts effects due to treatment (ezetimibe 10 mg, placebo), dose (simvastatin 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.	
Comparison groups	Ezetimibe + Simvastatin - Pooled v Simvastatin Monotherapy - Pooled
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	ANOVA
Parameter estimate	Difference in Least-squares Means
Point estimate	-12.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.29
upper limit	-9.18

Secondary: Percentage Change from Baseline in HDL-C

End point title	Percentage Change from Baseline in HDL-C
End point description:	
Serum HDL-C levels measured at baseline and after 6 weeks of study drug administration. Least-square means and standard errors calculated using an analysis of variance (ANOVA) model that extracted effects due to treatment (ezetimibe 10 mg, placebo), dose (simvastatin 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.	
End point type	Secondary
End point timeframe:	
Baseline and Week 6	

End point values	Ezetimibe + Simvastatin - Pooled	Simvastatin Monotherapy - Pooled		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126	120		
Units: Percentage Change				
least squares mean (standard error)	6.58 (± 1.16)	6.47 (± 1.19)		

Statistical analyses

Statistical analysis title	Difference in Percentage Change from Baseline
Statistical analysis description:	
Statistical comparison performed using an ANOVA model that extracts effects due to treatment (ezetimibe 10 mg, placebo), dose (simvastatin 10 mg, 20 mg, and 40 mg), treatment by dose interaction, and sex effects.	
Comparison groups	Ezetimibe + Simvastatin - Pooled v Simvastatin Monotherapy - Pooled
Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	ANOVA
Parameter estimate	Difference in Least-squares means
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.14
upper limit	3.35

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 53 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.1
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Reporting groups

Reporting group title	Ezetimibe + Simvastatin
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Reporting group description:

Participants who received ezetimibe coadministered with simvastatin in Period 1 and Period 2.

Reporting group title	Ezetimibe + Simvastatin - Long Term Experience
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Reporting group description:

Participants who received Ezetimibe + Simvastatin in Period 3 (Weeks 33 to 53)

Reporting group title	Simvastatin Monotherapy
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Reporting group description:

Participants who received simvastatin monotherapy in Period 1 and Period 2.

Serious adverse events	Ezetimibe + Simvastatin	Ezetimibe + Simvastatin - Long Term Experience	Simvastatin Monotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 126 (3.17%)	3 / 227 (1.32%)	1 / 122 (0.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 126 (0.00%)	1 / 227 (0.44%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental Overdose			
subjects affected / exposed	0 / 126 (0.00%)	0 / 227 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Encephalopathy			

subjects affected / exposed	1 / 126 (0.79%)	0 / 227 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 227 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Tendonitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 227 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Subcutaneous Abscess			
subjects affected / exposed	0 / 126 (0.00%)	1 / 227 (0.44%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pilonidal Cyst			
subjects affected / exposed	0 / 126 (0.00%)	1 / 227 (0.44%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis Bacterial			
subjects affected / exposed	1 / 126 (0.79%)	0 / 227 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 227 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ezetimibe + Simvastatin	Ezetimibe + Simvastatin - Long Term Experience	Simvastatin Monotherapy
Total subjects affected by non-serious adverse events subjects affected / exposed	58 / 126 (46.03%)	42 / 227 (18.50%)	59 / 122 (48.36%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	16 / 126 (12.70%) 25	6 / 227 (2.64%) 6	16 / 122 (13.11%) 22
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	9 / 126 (7.14%) 9 8 / 126 (6.35%) 12	2 / 227 (0.88%) 2 2 / 227 (0.88%) 2	3 / 122 (2.46%) 3 4 / 122 (3.28%) 4
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	4 / 126 (3.17%) 4	5 / 227 (2.20%) 6	8 / 122 (6.56%) 9
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	4 / 126 (3.17%) 4	3 / 227 (1.32%) 3	9 / 122 (7.38%) 9
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	7 / 126 (5.56%) 10	0 / 227 (0.00%) 0	1 / 122 (0.82%) 1
Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 126 (6.35%) 9 27 / 126 (21.43%) 30	12 / 227 (5.29%) 12 16 / 227 (7.05%) 16	12 / 122 (9.84%) 14 27 / 122 (22.13%) 31

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2007	Added fusidic acid to the list of prohibited medications and referred investigators to consult the local labeling for ezetimibe or simvastatin for a complete list of prohibited concomitant therapies for each therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported